

## OPINION

# Can preimplantation genetic diagnosis improve success rates in recurrent aborters with translocations?

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**Preimplantation genetic diagnosis (PGD) for people suffering recurrent miscarriages is increasingly being performed worldwide. However, there is limited information on whether PGD can improve success rates in translocation carriers. We therefore compared pregnancy outcomes between PGD and natural pregnancy cases, reviewing the clinical research database. No improvement in the success rate at the first oocyte retrieval was evident in reciprocal translocation carriers. In the natural course of events, patients with translocations can hope for a baby in the long term. However, with PGD, rates can reach 68% after IVF failure and the duration to eventual birth may be shorter than with natural pregnancies. In the particular case of Robertsonian translocations, PGD may not be necessary because natural success rates are relatively good.**

*Key words:* preimplantation genetic diagnosis/recurrent miscarriage/reciprocal translocation/Robertsonian translocation

### Introduction

The number of centres performing PGD worldwide has been steadily increasing since its introduction over a decade ago (Handyside *et al.*, 1990). New technologies, including fluorescence *in situ* hybridization (FISH), can be used to reduce the risk of spontaneous abortion in women suffering recurrent miscarriages and the advent of commercially available probes labelled with fluorochromes has led to the possibility using screening for translocation and aneuploidy in PGD (Gianaroli *et al.*, 1999; Munne *et al.*, 2000).

An abnormal karyotype in either partner, especially one featuring a translocation, is considered to be cause of recurrent miscarriage (De Braekeleer *et al.*, 1990) and many papers have been published in this regard. De Braekeleer *et al.* analysed a computerized database covering 22 199 couples (44 398 individuals) generated from the literature on cytogenetic studies and arrived at a rate of 4.7% for chromosomal structural rearrangements in patients suffering two or more spontaneous abortions. Carriers of reciprocal translocations are speculated to have higher frequencies of spontaneous abortions. However, clinical miscarriage rates and subsequent pregnancy outcome for different abnormalities have not been reported in detail.

Munne *et al.* concluded that PGD could achieve a statistically significant reduction in the miscarriage rate from 95 to 13% (Munne *et al.*, 2000). However, to our knowledge there have been no case–control studies comparing miscarriage rates between PGD and natural pregnancies after parents have been diagnosed as carriers of translocations.

### Natural pregnancy outcome of translocation carriers

Actual miscarriage rates for individual abnormalities have not been systematically analysed previously and there is little information available concerning the prognosis of patients with a history of recurrent miscarriages with a translocation, or the karyotypes of aborted conceptuses. Three articles have recently been published concerning the natural pregnancy outcome in recurrent aborters with translocations (Carp *et al.*, 2004a; Goddijn *et al.*, 2004; Sugiura-Ogasawara *et al.*, 2004).

Sugiura-Ogasawara *et al.* studied 1284 couples (2568 individuals) with a history of two or more (2–12) consecutive first-trimester miscarriages (Sugiura-Ogasawara *et al.*, 2004) who became pregnant at least once and could be followed up between January 1986 and December 2002. Fifty-eight (4.5%) had translocations, 21 in the male and 37 in the female. Eleven had Robertsonian translocations (three in males and eight in females). In the non-Robertsonian cases, seven of 18 (38.9%) where the husband had a reciprocal translocation could have a baby subsequently, and eight of 29 (27.6%) with a reciprocal translocation in the wife. Total success rate for both male and female abnormalities was 31.9% (15 of 47) at the first pregnancy after ascertainment of translocation status. Cases who had a reciprocal translocation in either partner miscarried significantly more frequently than those without an abnormal karyotype in either partner (68.1 versus 28.3%, 335 of 1184). In 12 of the 18 cases with male (66.7%) and 20 of the 29 with female translocations (69.0%), a baby was successfully born within the follow-up period. Four of the 11 cases (36.4%) who had a Robertsonian translocation miscarried again, the rate being similar to that for couples with a normal karyotype.

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FISH analysis of semen from carrier men with translocations suggests that 46.9% exhibit alternate segregation in reciprocal translocations and 88.7% exhibit alternate segregation in Robertsonian translocations (Gardner and Sutherland, 2004). This result suggests that success rates should be much higher with Robertsonian than with reciprocal translocations. PGD of oocytes has also been performed in cases with female reciprocal translocations and an overall average of 71.0% abnormal embryos was found in embryo-biopsy female cases with reciprocal translocation (Munne *et al.*, 2000). This proportion is in line with the miscarriage rate of 72.4% observed in the report of Sugiura-Ogasawara *et al.* for females with reciprocal translocations (Sugiura-Ogasawara *et al.*, 2004).

Goddijn *et al.* described the subsequent pregnancy outcome of structural chromosome abnormalities, including Robertsonian, inversion and mosaicisms (Goddijn *et al.*, 2004). The success rate of reciprocal translocation could not be obtained from their article. They concluded that karyotyping of 1324 couples ascertained for repeated miscarriage did not yield an unbalanced fetal chromosome pattern. They focused on fetal outcome. Carp *et al.* examined the first pregnancy outcome after ascertainment of translocation carriers and reported that 19 of 44 (43.2%) carriers had a live birth (Carp *et al.*, 2004a). However, they also included Robertsonian translocations, for which the success rate would be expected to be higher than that for reciprocal translocations. It is important to distinguish the two types of translocation when the success rate is discussed.

**Pregnancy outcome in PGD cases**

Several papers have documented subsequent pregnancy outcome after PGD (ESHRE PGD Consortium Steering Committee, 2002; Simopoulou *et al.*, 2003; Chun *et al.*, 2004; Sermon *et al.*, 2005). Simopoulou *et al.* published the first paper focusing on pregnancy outcome, though it included only eight patients.

Chun *et al.* described details for 43 reciprocal and six Robertsonian translocation carriers separately, though it was unclear whether the patients consisted of only recurrent aborters (Chun *et al.*, 2004). They reported that 14 of the 43 (32.6%)

patients with reciprocal translocations succeeded in having a baby after 59 started cycles (mean age, 31.5 ± 4.0), while one of six (16.7%) patients with Robertsonian translocations had a baby after 11 cycles (mean age, 30.8 ± 3.5). The success rate (32.6%) with first-cycle PGD was similar to that (31.9%) with natural pregnancy reported by Sugiura-Ogasawara *et al.* for patients with reciprocal translocations (Sugiura-Ogasawara *et al.*, 2004). Regarding the Robertsonian cases, the success rate by natural pregnancy (63.6%) is much higher than that (16.7%) with first-cycle PGD.

The ESHRE PGD Consortium showed that 17 of 25 infertile patients (68.0%) had successful pregnancies after a total of 96 oocyte retrieval cycles in reciprocal translocation carriers (female age 34.0) (ESHRE PGD Consortium Steering Committee, 2002). This means that around two-thirds of patients can have a baby after approximately four oocyte retrievals (Table I). The success rate of collection III was the highest among all collections to date [I–IV; ESHRE Preimplantation Genetic Diagnosis (PGD) Consortium 1999, 2000, 2002; Sermon *et al.*, 2005], the 68% with PGD being equal to the cumulative success rate of 68.1% with natural pregnancy.

Regarding Robertsonian translocation, the ESHRE PGD Consortium data collections I–III showed that 23 of 62 infertile patients (37.1%) had successful pregnancies after a total of 114 oocyte retrieval cycles (Sermon *et al.*, 2005). The success rate with PGD was thus lower than natural success rate of 63.6% at the first pregnancy after ascertainment of Robertsonian translocation status.

Five of 25 patients (20.0%) in the ESHRE study and five of 43 patients (11.6%) reported by Chun *et al.* experienced both chemical and clinical miscarriages in spite of PGD (Chun *et al.*, 2004). Whereas PGD could reduce the miscarriage rate compared with natural pregnancy, the eventual success rates were 68.0 and 68.1%, respectively. Patients undergoing PGD suffer from IVF failure instead of miscarriages. The expense of oocyte retrieval needs to be taken into account. In addition, oocyte retrieval has side-effects such as ovarian hyperstimulation syndrome, and injury of vessels and organs as well as the known risks of anaesthesia. Patients feel deeply sad with a strong negative emotional impact if they fail to conceive by

**Table I.** Pregnancy outcome of reciprocal translocation carriers

	First pregnancy after ascertainment of carrier status		Cumulative success rate	
	PGD (Chun <i>et al.</i> , 2004)	Natural (Sugiura-Ogasawara <i>et al.</i> , 2004)	PGD (ESHRE III, 2002)	Natural (Sugiura-Ogasawara <i>et al.</i> , 2004)
患者数			25	47
No. patients	43	47	34	
Age (years)	31.5 ± 4.0	29.1 ± 5.6	96	
Cycles to oocyte retrieval	59		3.8	
Oocytes retrieved per patient			22	
Positive HCG	22			
Miscarriages	6			
Delivery	14	15	17 <sup>a</sup>	32
Success rate	32.6%	31.9%	(68.0%) IVF 3.8 times Not described	(68.1%) Miscarriage 1.3 (1.9) times
Time to success				23.3 (22.5) months

患者数でなく、不妊症だった症例数

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<sup>a</sup>Positive heart-beat.

IVF–embryo transfer (Verhaak *et al.*, 2001). On the other hand, it takes about 23 months for patients with reciprocal translocations to achieve success, and on average they experience a further 1.3 miscarriages in the natural course of events. Needless to say, a further miscarriage will have a major emotional impact (Aoki *et al.*, 1998). The time taken to achieve successful pregnancy with PGD would be expected to be shorter, though the time taken for 3.8 IVF-PGDs was not described in the previous report (ESHRE PGD, 2002). We must fully explain side-effects of IVF–embryo transfer and the emotional impact of IVF failure and allow patients to exercise their decision to choose PGD or natural pregnancy.

In the Sugiura-Ogasawara study the miscarriage rate was 14.8%, despite a normal or balanced karyotype (Sugiura-Ogasawara *et al.*, 2004). Three of five patients who experienced miscarriages not only had reciprocal translocations but also had antiphospholipid antibodies (aPL), which may cause karyotypically normal abortion. Chun *et al.* reported one miscarriage and two ectopic pregnancies in 20 cases, despite a normal or balanced karyotype (Chun *et al.*, 2004). There are many causes of recurrent miscarriage, including aPL, uterine anomalies and immunological abnormalities. Different factors may interact and examinations should be performed systematically before subsequent pregnancy. Patients with both reciprocal translocations and aPL should be treated with appropriate anti-coagulant therapy.

Recently, Platteau *et al.* conducted a prospective study concerning PGD in unexplained recurrent spontaneous aborters without chromosome abnormalities in either partner (Platteau *et al.*, 2005). Of the blastomeres derived from patients younger than 37 years and 37 years or older, 43.85 and 66.95% were abnormal, respectively. Clinical pregnancy rates after PGD were 9/25 (36%) and 1/24 (4.2%) in these age groups of patients suffering idiopathic recurrent miscarriage.

Carp mentioned that PGD is indicated in the older age group because their abnormal embryonic karyotype rate is higher than in the general population (Carp *et al.*, 2004b). In fact, abnormalities were found to be higher in the older group in the Platteau's study. However, there are patients who repeat miscarriage with an abnormal embryonic karyotype and with a normal karyotype included in unexplained recurrent aborters. The pregnancy prognosis of the former is better. Thus, the incidence of abnormal embryonic karyotypes decreases as the number of miscarriage increases. PGD would be useful for patients who demonstrate repeated miscarriages with abnormal embryonic karyotypes. In contrast, it would not be effective for patients who repeat miscarriages with a normal embryonic karyotype, who are also severe cases.

We do not believe that PGD is useful for patients with unexplained recurrent miscarriage without translocations because the pregnancy prognosis of patients who repeat miscarriages caused by an abnormal karyotype is relatively good. The overall success rate for subsequent pregnancy is 70% in patients with three previous miscarriages and 60% in patients with four previous miscarriages after examination and conventional treatment (Ogasawara *et al.*, 2000). However, the success rate with PGD was only 36% in patients younger than 37 years in Platteau's study.

Regarding translocations, success rates would be lower at higher ages because fewer oocytes can be obtained and the success rate of IVF itself would be lower. Also, the older patients do not have time to wait for natural success.

The miscarriage rate can be expected to differ among individuals. A chromosome with a reciprocal translocation forms a quadrivalent with matching homologous segments at meiosis I (Gardner and Sutherland, 1996). There then follows alternate segregation, adjacent-1, adjacent-2, 3:1 segregation and 4:0 segregation. Patients who succeed at the first PGD could be expected to succeed naturally because the success rate depends on the rate of alternate segregation. However, for women with higher age or a high number of previous miscarriages, IVF-PGD might be able to save time and facilitate having a baby. In future studies we must find out who has difficulty in reaching successful delivery among recurrent aborters with reciprocal translocations. For example, male carriers should undergo PGD when FISH analysis of semen shows a low frequency of alternate segregation.

## Conclusion

Overall, PGD cannot improve success rate at the first oocyte retrieval in recurrent aborters with reciprocal translocations and in the natural course of events. Affected patients can hope for a baby in the long term. However, PGD rates can reach 68% after IVF failure and the duration is shorter than that with natural pregnancy. In the particular case of Robertsonian translocations, PGD may not be necessary because natural success rates are relatively good. In all cases, systematic examinations should be performed before subsequent pregnancy because different factors may interact to determine the eventual outcome.

Patients should receive proper information regarding advantages and disadvantages, such as the possible impairment of embryo viability by using the PGD technique. The impact of going through another miscarriage should not be underestimated. After receiving the information, couples can decide with the clinician on whether to perform PGD. PGD is still a relatively new technique and the impact of removing one or two blastomeres at eight-cell stage on adulthood has still not been sufficiently evaluated, and such an approach should be proposed for well-selected cases only. In future studies, we must identify those with difficulty in reaching successful delivery amongst recurrent aborters with translocations.

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